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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,005	09/19/2003	Kamil Paruch	OC01625K	5836

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SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530

EXAMINER

RAO, DEEPAK R

ART UNIT

PAPER NUMBER

1624

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
10/665,005	PARUCH ET AL.	
Examiner	Art Unit	
Deepak R Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 31 March 2004.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-20 and 24-29 are pending in the application.
 4a) Of the above claim(s) 3,4,9 and 13-16 are withdrawn from consideration.
 5) Claim(s) 18 is/are allowed.
 6) Claim(s) 1,2,5-8,10-12,17,19,20 and 24-29 are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date 40504.

4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on March 31, 2004.

Claims 1-20 and 24-29 are pending in this application.

Election/Restrictions

Applicant's affirmation of the election with traverse of the species of Example 21 in the reply filed on March 31, 2004 is acknowledged. The traversal is on the ground(s) that a restriction within claim 1 is inappropriate because they form part of one common invention.

An election of species following MPEP § 803.02 guidelines was made in the application and no division into groups of invention was made. (Applicant's attention is directed to page 4 of the previous office action wherein the portion of MPEP was provided). The guidelines indicate that 'if prior art is found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected **and claims to the nonelected species held withdrawn from consideration**'. In the previous office action it was clearly indicated how the search was expanded, which has been acknowledged by the applicant. The claims not encompassing the limitations of the subgenus that was considered for examination are withdrawn from consideration as per the guidelines. For example, claim 3 recites that R is H and the search and examination was based on compounds wherein R is 2-chlorophenyl and therefore, claim 3 was held withdrawn from consideration. As the specific claims 3-4, 9 and 13-16 recite limitations other than those included in the subgenus around which a search and examination has been performed, these claims are withdrawn from further consideration.

The following rejections are withdrawn:

The rejection under 35 U.S.C. 112, second paragraph of the previous office action is withdrawn in view of the amendment.

The rejection under 35 U.S.C. 112, first paragraph for claims 21-23 is rendered moot by cancellation of the claims. The rejection for other claims is maintained along with claim 24 which is rejected under new grounds, for the reasons provided below.

The following rejections are maintained and/or under new grounds:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20 and 24-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting CDK2 and/or a method of treatment of specific cancers (recited in claim 24), does not reasonably provide enablement for inhibiting all types of cyclin dependent kinases or for the treatment of all other diseases embraced by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the

art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims are drawn to “a method of treating one or more diseases associated with cyclin dependent kinase CDK2” which according to specification are drawn to a therapeutic use, e.g., in treating proliferative diseases, autoimmune diseases, viral diseases, inflammation, etc. (see page 20). First, the instant claims cover ‘diseases’ that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Test assays and procedures using CDK2 containing cells are provided in the specification pages 61-62, related to CDK2 inhibition, wherein the CDK inhibitory activity data (in terms of IC₅₀ in μ M range) for some of the compounds of the invention is provided in Table 7, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the disorders of the instant claims. The disorders encompassed by the instant claims include proliferative disorders or cancers which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how the patient in need of such specific kinase inhibiting activity is identified and further, how types of proliferative diseases are treated. See

MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the data provided of the single compound is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. Regarding CDK mechanism, Blain et al. (J. of Biol. Chem.) report that “their specific functions are still poorly understood” (see page 25863, col. 1). Also, LuValle et al. (Frontiers in Bioscience) express that “detailed analyses of these pathways are necessary for a complete understanding of chondrocyte proliferation and differentiation” (see page 5, section 4). This is clearly indicative of the fact that the therapeutic role of these kinase inhibitors is very speculative.

A ‘proliferative disorder’ is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a “silver bullet” is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that “each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment

and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

Enablement for the scope of "inflammation" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science.

Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with

mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation and further, establishes that it is not reasonable to any therapeutic agent to be able to treat inflammation generally.

It is inconceivable as to how the claimed single class of compounds can treat viral diseases generally. For example, there is no known common therapeutic mechanism for viral diseases generally. There are more than 400 distinct viruses that infect humans producing a wide range of diseases. The Merck Manual of Diagnosis and Therapy states that "Several hundred different viruses infect humans. Because many have been only recently recognized, their

clinical effects are not fully understood" and "Only a few viral diseases can be diagnosed clinically or epidemiologically" see

<http://www.merck.com/mrkshared/mmanual/section13/chapter162/162a.jsp>. Cecil Textbook of Medicine states that "for many viral infections, no specific therapy exists. Proper use of antivirals requires specific viral diagnosis" (see the enclosed article, page 1742).

Claim 24 is drawn to treatment of various types of diseases – cancer of the bladder, breast, colon, etc.; several types of leukemia, sarcoma, etc. and there is no established single antiproliferative therapeutic agent for all these types of diseases. The ideal chemotherapeutic drug would target and destroy only cancer cells without adverse effects or toxicities on normal cells. Unfortunately, no such drug exists; there is a narrow therapeutic index between cell kill of cancer cells and that of normal cells. Successful treatment of cancer requires elimination of all cancer cells, whether at the primary site, extended to local-regional areas, or metastatic to other regions of the body. The major modalities of therapy are surgery and radiotherapy (for local and local-regional disease) and chemotherapy (for systemic sites). For example, regarding the treatment of leukemia, The Merck Manual (online edition) states that "Treatment programs and clinical situations are complex". Dosage regimen is dependent on several risk factors and the contribution of each active ingredient of a multidrug combination therapy is complex and unclear. Similarly, Myelodysplastic syndrome (MDS) is characterized by clonal proliferation of hematopoietic cells, including erythroid, myeloid, and megakaryocytic forms and its incidence is unknown and further, there is no established treatment. Several growth factors and their receptors have been associated with glioma and the treatment depends on the pathology and location and is often multimodal.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved”. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Applicant’s arguments in the response filed on March 31, 2004 have been fully considered but they were not deemed to be persuasive. Applicant relies on Background of the Invention to provide sufficient enablement for the linking CDK2 inhibition activity to treatment of various diseases. However, the references cited in the specification do not provide such nexus. See e.g., Vesely et al., discusses the activity of olomoucine and conclude that “olomoucine may lead to a compound which will preferentially inhibit the proliferation of

certain tumor cells", there is nothing in the reference that these class of compounds are useful against all types of diseases, including various types of cancers of the instant claims.

Senderowicz et al., indicate that "Despite efforts over several decades that used standard antineoplastic agents as single agents or in combination, the improvement of the prognosis for patients with advanced prevalent neoplasms (eg. lung, breast, prostate, and colon) remains a formidable challenge". The reference concluded that 'an antitumor effect was observed in certain patients with renal, prostate and colon cancer'. Even applicants acknowledge the fact that 'pharmaceutical art is notoriously unpredictable'. Therefore, there is nothing in the Background of the invention establishing that the claimed single class of compounds be useful in the variety of diseases encompassed by the instant claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 8, the term "2-ylpropanol" is not understood. It is not clear what the number 2 is referring to. The recitation does not appear to be consistent with nomenclature.
2. In claim 24, the recitation "skin, **including** squamous cell carcinoma" is confusing. It is not clear what is intended by the preferred recitation of the specific disease as part of skin cancer.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-2, 5-8, 10-12, 17, 19-20 and 24-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns et al., WO 02/060492. The reference teaches a generic group of imidazo[1,2-a]pyrazine compounds that are useful as therapeutic agents having kinase inhibitory activity, see formula II in page 10 and the corresponding species in Table 7, particularly compound 57 (page 56, last compound) and the activity in page 16, starting at line 19. Some of the instant claims recite that R² is alkyl, e.g., methyl, as compared to the reference compound which is unsubstituted at the analogous position. Since the instant compounds differ by having a methyl group in place of the hydrogen disclosed for reference compounds (i.e., differing by a -CH₂ group), the instantly claimed compounds are homologs of the reference compound. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds would be expected to possess similar utilities. It has been held that compounds that are structurally homologous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results. *In re Haas*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950).

Applicant's arguments filed in the response dated March 31, 2004 have been fully considered, but they were not deemed to be persuasive. Applicant's arguments based on the references submitted in Exhibits A and B are fully considered. However, neither of the references showed structurally analogous compounds. Exhibit A discloses 1,4-diazepine attached to a isoquinoline through a -SO₂- group and Exhibit B discloses 4-pyrid-3-yl-2-

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anilinopyrimidine compounds. The instantly claimed compounds on the other hand are drawn to imidazo[1,2-a]pyrazine compounds which structurally very different from the compounds discussed in the references. The instantly applied reference also teaches compounds having the identical nucleus, and only differing by a methyl substituent. The reference also teaches the use of the compounds in treatment of diseases such as cancer, etc. Therefore, the reference provides sufficient motivation to one of ordinary skill in the art to prepare the homologous compounds.

Applicants have not provided any unexpected results for the claimed compounds when compared to the reference compounds. The discussion of the references in Exhibits A and B is not commensurate in scope with the instantly claimed compounds. Accordingly, the rejection is maintained.

Allowable Subject Matter

Claim 18 is allowed. The references of record do not teach or fairly suggest the claimed compounds.

Information Disclosure Statement filed on April 5, 2004 is acknowledged and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Deepak Rao
Primary Examiner
Art Unit 1624

June 13, 2004